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Impact of intraoperative MRI-guided transsphenoidal surgery on endocrine function and hormone substitution therapy in patients with pituitary adenoma

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Abstract: **BACKGROUND:** Pituitary adenomas are rare with an incidence of 0.4-8.2 per 105 inhabitants. Symptoms range from headaches to pituitary insufficiency or excessive output of hormones with associated disease. Except for prolactinomas, surgery is recommended as the first line and most effective treatment for the majority of these tumours. One of the refinements of surgical therapy introduced was intraoperative magnetic resonance imaging (iMRI). **OBJECTIVE:** The aim of this study was to analyse the postoperative pituitary function and the general outcome of patients treated for non-functioning and GH-producing pituitary adenomas with a transsphenoidal iMRI-assisted approach using the PoleStar™ N20 imager. **METHODS:** A total of 148 consecutive iMRI-guided surgeries for GH-producing and non-functioning pituitary adenomas were retrospectively analysed. Patients' clinical data, endocrinological parameters, clinical examinations and pre-/post- and intraoperative imaging studies were evaluated. **RESULTS:** A total of 101 patients could be classified as being in remission at follow-up; 26 (17.6%) of them due to iMRI allowing additional tumour removal. A total of 44 patients (29.7%) had more complete tumour removal because remnants were detected by iMRI. The mean hormone levels of patients did not differ significantly between pre- and postoperative examinations. There were 62 patients with preoperative, and 43 patients with postoperative pituitary insufficiency, thus, due to surgery there were 19 (12.8%) patients with improved pituitary function. **CONCLUSIONS:** The results show this method to be a safe and effective treatment option increasing remission rate and keeping complication rate low. Postoperative pituitary function was preserved or improved - possibly due to more exact iMRI-assisted tumour removal.

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Impact of intraoperative magnetic resonance imaging-guided transsphenoidal surgery on endocrine function in patients with pituitary adenoma

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1. Abstract:

Background: Pituitary adenomas (PA) are rare with an incidence of 0.4 – 8.2 per 10⁵ inhabitants. Symptoms range from headaches to pituitary insufficiency or excessive output of hormones with associated disease. Except for prolactinomas, surgery is recommended as first line and most effective treatment for the majority of these tumors. One of the refinements of surgical therapy introduced was intraoperative magnetic resonance imaging (iMRI).

Objective: The aim of this study was analyzing the postoperative pituitary function and the general outcome of patients treated for non-functioning and GH-producing PAs with a transsphenoidal iMRI-assisted approach using the PoleStar™ N20 imager.

Methods: 148 consecutive iMRI-guided surgeries for GH-producing and non-functioning PAs were retrospectively analyzed. Patients' clinical data, endocrinological parameters, clinical examinations and pre-/post- and intraoperative imaging studies were evaluated.

Results: 101 patients could be classified as being in remission at follow-up; 26 (17.6%) of them due to iMRI allowing additional tumor removal. 44 patients (29.7%) had more complete tumor removal because remnants were detected by iMRI.

The mean hormone levels of patients did not differ significantly between pre- and postoperative examinations. There were 62 patients with preoperative- and 43 patients with postoperative pituitary insufficiency, thus, due to surgery there were 19 (12.8%) patients with improved pituitary function.

Conclusions: The results show this method to be a safe and effective treatment option increasing remission rate and keeping complication rate low. Postoperative pituitary function was being preserved or improved - possibly due to more exact iMRI-assisted tumor removal.

Keywords:

Acromegaly, PoleStar™ N20, intraoperative magnetic resonance tomography, MRI, iMRI, pituitary adenoma, transsphenoidal surgery, non-functioning pituitary adenoma, endocrinological outcome, endocrinology

2. Introduction:

Pituitary adenomas (PA) are rare neoplasm with an estimated incidence of 0.4 – 8.2 per 10^5 inhabitants (1,2,3). Symptoms range from headache and cranial nerve palsy – being signs of elevated intracranial pressure or direct compression of neural structures (4,5) - to endocrinological deficiency or excessive output of hormones with associated disease (6,7). Diagnosis is usually established by computed tomography (CT) or magnetic resonance imaging (MRI) performed for investigation of neurological symptoms or endocrinological disturbances and endocrinological examination including hormone blood levels.

Acromegaly is a rare disease with an estimated incidence of about 4 per 10^6 inhabitants. In most cases, it is caused by a growth-hormone (GH)-producing pituitary adenoma (PA). If excessive output of GH is not normalized, severe cardiovascular and metabolic disturbances as well as cosmetic and orthopaedic deformities will result. Previously published studies have shown a 2-3-fold increased mortality for treatment-resistant cases as compared to successfully treated patients and healthy individuals (8,9,10). Correction of GH values to normal can restore life expectancy towards normal. First surgical treatment using a transnasal approach in an acromegalic patient was performed by Dr. Schloffer in Vienna in 1907 (11).

Non-functioning pituitary adenomas (NFPAs) add up to (nowadays 30-50% of all macroadenomas) 25-30% of all PAs with an estimated incidence of 0.1 – 3.0 per 10^5 inhabitants (7,12,13). The symptoms of NFPAs are caused by the tumor's mass effect, which results in headache due to stretching of the diaphragma sellae and the sellar dura and visual deficits due to chiasmal compression. Diplopia may occur as a result of lateral tumor growth and/or hemorrhage into the cavernous sinus. In addition, patients can develop symptoms of secondary pituitary insufficiency due to compression of the pituitary gland (6,7). Visual disturbances occur in 53.8-74% (4,5) headaches in 9.7-56% (4,14), and third nerve palsy in 12% (4).

Except for asymptomatic micro-PAs and for prolactinomas, surgery is generally recommended as treatment of choice (1,6,15,16,17,18,19,20,21). As most pituitary

adenomas are benign neoplasms, tumor control can be achieved by complete resection. Today, most patients receive surgery as first line treatment using a transnasal, transsphenoidal approach introduced by Cushing (22) and reintroduced using microsurgical techniques by Hardy in 1979 (23). In cases successfully treated by surgery, the outcome is defined by persisting neurological symptoms and pituitary function. A requirement for hormone replacement therapy is associated with the inconvenience of daily medication and regular tests whether the treatment is appropriate; moreover, hormone substitution is also an important socioeconomic factor as replacement therapy can generate costs being a multiple of the initial surgical treatment.

In recent years there have been a lot of refinements in the surgical treatment of PA like improvement of endoscopy and introduction of intraoperative magnetic resonance imaging (iMRI) (21,24,25,26,27,28,29,30,31,32,33). Those treatment options have been analyzed regarding the clinical outcome and tumor control and showed superior results in the treatment of certain PAs (i.e. Growth hormone producing PA) compared to the conventional surgical approach. Endocrinological outcome has only been a minor part in those studies as the research focus concentrated mainly on tumor control.

In this largest study to date we analysed the postoperative pituitary function and the general outcome of 148 consecutive surgical procedures for non-functioning and GH-producing PAs being treated using a transnasal, transsphenoidal microsurgical iMRI-assisted approach using the PoleStar N20 imager.

3. Patients and methods

3.1. Patient demographics (Table 1):

One-hundred-forty-eight surgical procedures were performed in 145 patients (82 male, 63 female) suffering from non-functioning- or GH-producing PA between September 2005 and August 2009. Thirty-nine patients presented with GH-producing PA and 109 patients with NFPA. Three patients (1 male, 2 female) underwent surgery twice for removal of recurrent tumor. All patients were being operated by the senior author R.L.B. using the same standardized transsphenoidal approach with the aid of ultra low-field iMR imaging. The mean patient age was 55 ± 15 years (range 19–80 years). The median preoperative tumor volume was 6797 mm³ (range 50–65,450 mm³; mean diameters

23mm*20mm*19mm). Ten cases (6.9%) presented with microadenomas, 118 (82.5%) with macroadenomas, and 15 (10.5%) with giant adenomas. 24 patients (17.1%) had previous pituitary surgery. In 51 cases (35.7%) the tumor invaded the cavernous sinus. Overall, 89 patients (62.2%) had cranial nerve symptoms, among them 79 (55.2%) with visual field deficits. 56 patients (37.8%) complained about headache. In 37 out of the 39 cases (94.8%) with GH-producing PA, patients had symptoms of acromegaly.

3.2. Pre- and postoperative management:

Patients were seen as outpatients before surgery. After decision for surgical treatment, patients arrived in hospital the day before surgery. Preoperative diagnostics included computed tomography (CT) scan and magnetic resonance imaging (MRI) for determination of the pituitary adenoma, bony and neurovascular structures. Pre- and postoperative imaging studies were performed at the Department of Neuroradiology, University Hospital of Zurich. CT studies were performed on a 16 slice CT scanner (Siemens SOMATON® Sensation, München, Germany) acquiring non contrast-enhanced and contrast-enhanced multi slice imaging data. The MRI studies were performed on a 1.5 Tesla MR tomography scanner (Signa®, General Electric, Milwaukee, USA).

Neurological and ophthalmological examinations were performed after admission. General patient data, additional diagnosis, medication at admission and previous study results were noted. Patients underwent endocrinological examination which included blood analysis for pituitary function examining growth hormone (GH), insulin-like growth factor-1 (IGF-1), adrenocorticotropin (ACTH), cortisol, thyroid stimulating hormone (TSH), fT4, fT3, prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH) and human chorionic gonadotropin (hCG); testosterone was measured in male and estradiol in female patients unless a history of recent menstrual bleedings or of contraceptive pill intake was given.

Patients signed written consent for the surgical procedure and general anaesthesia. At the day of surgery, patients with reduced Cortisol plasma levels received 100mg hydrocortisone (SoluCortef®, Pfizer, New York City, USA) one hour before operation, and another dose of 100mg hydrocortisone was given perioperatively. After surgery, patients were transferred to intermediate care unit (IMCU). A postoperative CT scan was performed in all patients around six hours after surgery to exclude major bleeding or serious complications. The next morning patients were transferred to the general ward and mobilized. They received 100mg of hydrocortisone on the first and 50mg on the

second postoperative day. On the morning of the third operative day and/or before discharge, pituitary function was re-examined. If patients' cortisol levels were below 200nmol./l in early morning blood samples, they received 30mg of hydrocortisone (Hydrocortone®, Merck, Darmstadt, Germany) per day until endocrinological follow-up as outpatients four weeks after surgery.

3.3. Surgery and intraoperative neuroimaging:

All operations were performed in general anaesthesia. Patients were put in supine position on a foldable standard operation table with their head slightly reclined. The head was then fixed in a MRI-compatible head holder after adjusting the radio frequency coil around the patients head. The iMRI scanner used in all patients was a PoleStar™ N20 (0.15 Tesla, Medtronic Navigation, Louisville, CO, USA). Afterwards the intraoperative navigation system (Stealth Station, Medtronic Navigation, Louisville, CO, USA) was referenced with preoperative CT studies. The position of the patient's head in the scanner was tested by performing a 24 second sagittal e-steady scan (8mm slices) and adjusted if necessary. Before surgery, a 7-minute, T1-weighted, gadolinium (20 ml Dotarem®, Guerbet, Roissy CdG Cedex, France) enhanced, 4mm slice, coronal iMRI scan was performed. These images were automatically loaded into the navigation system and merged with the preoperative imaging studies.

All parts of surgical procedures were performed by using an operating microscope (Pentero®, Carl Zeiss, Oberkochen, Germany). At the beginning of operations a self-retaining endonasal speculum was inserted in the nostril chosen for surgical approach. The mucosa was incised and partially removed, the posterior bony part of the septum was removed and the anterior wall of the sphenoid sinus was displayed. The anterior wall of the sphenoid sinus was then opened with punches, the intrasphenoidal mucosa and septum were removed and the inferior and anterior surface of the sella was displayed and opened with a chisel. The dura mater was opened in an x-shaped fashion and the adenoma removed by curettes, grasping forceps and suction devices. Tumor material was sent for frozen sections and neurohistopathological examination. After complete tumor removal according to the surgeon's impression, a 3.5-minute, T1-weighted, gadolinium-enhanced, 4mm slice, coronal iMRI scan was performed for resection control in all patients. For better visualisation of possible tumor remnants, a glove-covered ball of bone wax was inserted into the resection cavity for hemostasis and improved interpretation of intraoperative images. The intraoperatively acquired images were automatically merged

with the existing preoperative and intraoperative imaging studies. In cases of visible tumor remnant, the resection cavity was re-examined and tumor remnants removed if possible. Another post-resectional, intraoperative 3.5-minute, T1-weighted, gadolinium- enhanced, 4mm slice, coronal iMRI scan was performed in those cases. The anterior wall of the sella turcica was reconstructed by using the extracted posterior part of the bony nasal or intrasphenoidal septum. In cases of intraoperative CSF leakage, the sella was packed with abdominal fat and use of fibrin sealant. No nasal packing was used. All operations were performed by the senior author.

3.4. Follow-up:

All patients were followed-up four weeks postoperatively as outpatients in the endocrinology clinic; hormone levels were analyzed and deficiencies replaced if necessary. Three months after surgery, patients received a postoperative MRI study for resection control and patients were seen for neurosurgical follow up and examination.

3.5. Statistical analysis and neuroimaging:

The statistical analysis was performed using Microsoft Excel (Version 2003) and SPSS Statistic software (Version 16.0). All imaging studies were analyzed independently and blinded to the clinical outcome using standardized software (picture archiving and communication system, PACS). Tumor volume was calculated based on the diameter method ($\text{Tumor volume} = \frac{4}{3} * \pi * \frac{1}{2}x * \frac{1}{2}y * \frac{1}{2}z$), where x, y and z are the maximum diameters in the three axis.

4. Results

4.1. Intraoperative imaging: (Table 2)

On average, 2.51 ± 0.99 intraoperative imaging studies were acquired per patient; the first at the beginning of the surgical procedure for mapping with the preoperative high-field MRI and a CT study, and another scan was performed before closure to confirm tumor removal and to check for tumor remnant. Based on these images, 44 patients (29.7%) received further tumor removal since tumor remnants were detected. In this case, at least one further imaging study was made to check for further tumor remnant. The other 98 patients (66.2%) showed no sign of tumor remnant (86 patients) unless visible tumor

remnant was left in place (12 patients) due to predictably high risk of complications in case of further tumor removal. There was a rate of patients being in remission during the overall follow-up in this study of 75.5% within the group of patients not undergoing further tumor removal and of 59.1% in the group undergoing further tumor removal. There were an additional 26 patients (17.6% of study group) being in remission during follow-up due to intraoperative imaging that lead to complete adenoma resection.

4.2. Neurodiological follow-up: (Table 2)

Patients were seen for clinical and neuroradiological follow-up (1.5 Tesla MRI) at three months after surgery. There was another MRI performed one year postoperatively, and further imaging studies during overall follow-up in case of visible tumor remnant, tumor regrowth or newly developed symptoms. Overall mean follow-up during this study was 32 month (range 4-62 month).

There were 106 patients considered tumor remnant-free, and 101 of them were considered in remission. The remaining 5 patients underwent surgery for GHPA and postoperatively complained about persisting symptoms of acromegaly and suffered from elevated GH levels without showing tumor remnant in postoperative high-field MRI.

There were 42 patients with postoperative tumor remnant visible in postoperative high-field follow-up MRI. The mean volume of tumor remnant was 1191mm^3 (range 4-15559 mm^3). The tumor volume could be reduced to around one sixth of the preoperative size (6797mm^3 (range 50-65,450 mm^3)) in those patients.

4.3 Early postoperative course and complications:

Patients were hospitalized for a mean (mit range eher median geben als mean) time of 9 days (range 5-79 days). Six patients needed temporary lumbar drainage and one patient a temporary external ventricular drainage due to postoperative cerebrospinal fluid (CSF) fistula. Ten patients developed postoperative transient diabetes insipidus (DI) with the need of temporary treatment with desmopressin during hospitalization of which one needed permanent medication. Eight patients developed temporary SIADH within the first 24 days after surgical treatment with need for further or ongoing hospitalization. Three patients needed transsphenoidal revision surgery for CSF fistula with associated meningitis and one for CSF fistula alone.

Two patients died during the study period for reasons considered unrelated to the surgical procedure (one for unknown reasons 11 months after surgery at an age of 87 years, one for pneumonia at an age of 59 years 2 months after surgery).

4.4. Endocrinological outcome:

Patients underwent endocrinological examination pre and postoperatively (Table 3). The mean hormone levels of cortisol, TSH, fT4, GH, IGF1 and prolactin did not differ significantly between the pre- and the postoperative condition. Mean cortisol level in nmol/l was 393 (3-1640) and 349 (9-808); mean TSH level in mU/l was 1.73 (0.01-6.96) and 1.72 (0.01-6.12); mean fT4 level in pmol/l was 13.80 (5.60-20.30) and 15.35 (4.00-25.40); mean GH level in NFPA patients in ug/l was 0.59 (0.05-4.88) and 1.21 (0.08-5.55); mean IGF1 level in NFPA patients in ug/l was 102 (31-492) and 101 (29-209) and mean prolactin level in ug/l was 25.07 (0.50-109.50) preoperatively and 15.38 (0.50-227.00) postoperatively .

Before surgery, 62 patients (41.9%) were found with partial or total pituitary insufficiency of which only 30 patients (48.4%) received preoperative hormone substitution therapy – in many cases due to the short time between diagnosis and surgery (Table 4); GH deficiency was usually not sought by provocative tests and is therefore underreported. 38 (61.3%) of these 62 patients had persisting pituitary insufficiency, with need for ongoing hormone replacement therapy after surgery, but in 25 patients (38.7%) postoperative examinations showed full recovery of pituitary function without signs of insufficiency or further need for substitution therapy. 21 out of these 25 patients (87.5%) were patients with NFPAs without previous pituitary surgery who underwent further tumor removal due to intraoperative imaging. There were statistically no significant differences in Hardys classification of these patients.

Among the 62 patients with preoperative pituitary insufficiency, 22 (35.5%) had a PA invading the cavernous sinus. In the group with postoperatively persisting insufficiency, 14 patients (36.8%) had preoperative tumor infiltration of cavernous sinus. In the group with full recovery of pituitary function the rate was roughly the same with 8 patients (33.3%) showing infiltration of cavernous sinus.

In contrast to the above mentioned group with full recovery of pituitary function, there were 13 patients (8.8%) who developed pituitary insufficiency after surgery and required (at

least temporarily) hormone substitution therapy. All these patients had NFPA's. Five of them were in need of permanent hormone substitution therapy. These five patients were all considered not being in remission after surgical procedures during this study. Interestingly there was not one single case with first time pituitary surgery and postoperative newly developed persisting pituitary insufficiency. Only one of them showed PA infiltration of cavernous sinus in preoperative imaging.

Analysis of pituitary function in patients grouped according to the PA's Hardy classification of their adenoma revealed that those in class D and E were more severely affected than those in classes A, B and C. Before surgery we found pituitary insufficiency in 10 patients (30.3%) of class A, in 24 patients (42.1%) of class B, in 10 patients (30.3%) of class C, in 11 patients (68.7%) of class D and in 7 patients (77.8%) of class E. In all those groups roughly half of the patients were on hormone substitution therapy when admitted to hospital for surgical treatment – 5 patients (15.1%) of class A, 12 patients (21.0%) of class B, 6 patients (18.2%) of class C, 5 patients (31.2%) of class D and 3 patients (33.3%) of class E.

After surgery, improving pituitary function was more often observed than deterioration, i.e. overall, disappearance of pituitary insufficiency was more common than development of pituitary failure. 24 patients with insufficiency at baseline no longer needed hormone substitution therapy after surgery: – 6 (18.2%) of class A, 8 (14.0%) of class B, 4 (12.1%) of class C, 5 (31.2%) of class D and 1 (11.1%) of class E according to Hardys classification.

On the other hand, 13 patients, considered sufficient at baseline, developed pituitary insufficiency after surgery. Five of them suffered from permanent insufficiency and remained dependent on long term hormone replacement therapy – 2 (6.1%) of class A and 3 (5.3%) of class B according to Hardys classification.

The remission rates in the different patient groups were 72.7% for class A, 77.2% for class B, 69.7% for class C, 25.0% for class D and 66.6% for class E according to Hardys classification.

Overall, there were 62 patients with pituitary insufficiency before surgery; 30 of them were on hormone replacement treatment. Overall, there were 43 patients with postoperative pituitary insufficiency and need for ongoing hormone substitution therapy – 5 with newly

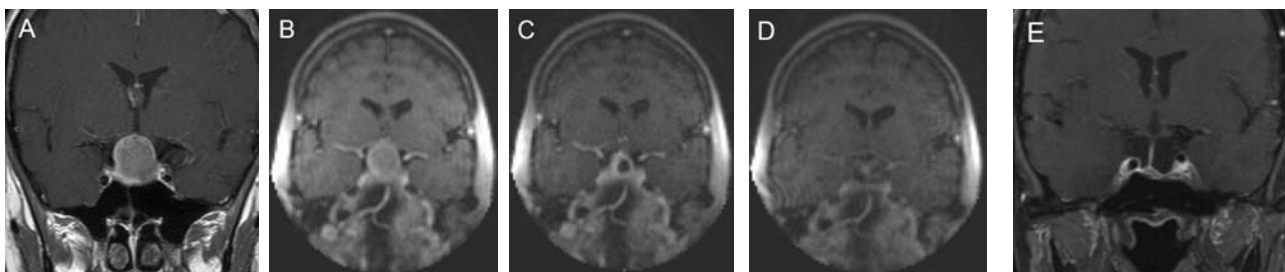
developed insufficiency postoperatively and 38 with persisting insufficiency. Therefore, surgical treatment resulted in a net decrease of 19 patients who were in need for medical treatment in the postoperative as compared to the preoperative condition; – 30.6% of the patients with preoperative pituitary insufficiency and 12.8% of the complete study population.

4.5. Clinical outcome:

Patients were seen at three months follow-up for clinical-neurological examination. Out of 56 patients complaining about headache before surgery, 38 patients (67.8%) reported complete regression, 5 patients (8.9%) improvement and 13 patients (23.2%) unchanged pain. Regarding visual field deficits there was a complete regression found in 55 patients (69.6%), an improvement in 14 patients (17.7%) and unchanged symptoms in 10 patients (12.6%).

5. Illustrative Case:

A forty-two year old female was admitted for resection of a large pituitary adenoma. She complained about headache, amenorrhea and galactorrhea. Endocrinological diagnosis revealed a panhypopituitarism. The patient underwent surgery and the non-functioning pituitary adenoma could be totally removed. Postoperative follow-up showed normal pituitary function and the patient is in remission for 48 month by now. The figures show preoperative imaging, intraoperative imaging with various stages of the tumor resection and postoperative follow-up MRI.



6. Discussion:

In this largest study to date we analyzed the postoperative outcome, neurological symptoms and postoperative pituitary function in 148 patients undergoing iMRI-assisted transsphenoidal surgery for GH-producing- and NFPA.

The overall remission rate during a mean follow-up of 32 months (4-62) was 101 out of 148 patients (68.2%) applying the remission criteria of the latest international consensus conference regarding the GH-producing PAs and not detectable tumor remnant or regrowth in neuroradiological follow-up with high-field MRI in patients with NFPA. These results are as least as good as previously published series reporting remission rates between 25 and 70% (5,27,34,35,36,37,38,39,40,41). Comparison remains difficult as most of the series included all kind of PAs but did not include giant adenomas, and remission criteria differed widely.

Our results show that pituitary function was preserved in most of the patients as there were only 5 patients (3.4%) showing postoperative pituitary insufficiency and need for permanent medical treatment which is in accordance with the literature showing rates ranging from 5.6% to 30.0% (42). Mean hormone values showed no significant differences between pre- and postoperative endocrinological examinations in this study.

Adenoma resections even led to complete recovery of pituitary function in 24 patients so that overall, 19 patients (12.8%) less remained dependent on permanent substitution therapy. Comparison with other published series is difficult as patient groups, type of included adenoma and other study parameters differ widely.

Interestingly, remission rates were not related to postoperative need for further hormone substitution – which was already been shown in the literature (42). Among the patients with preoperative pituitary insufficiency, 36 patients were in remission while 26 patients were not. There was no need for further hormone substitution in 14 out of these 36 patients (38.9%) and in 10 out of those 26 patients (38.5%).

The surgical method used appeared safe as only a minor number of patients suffered complications. There were only four patients with need for reoperation because of CSF fistula and no patients with neurological deterioration due to surgery. The two deaths (one due to pneumonia) within the study population were considered unrelated to the surgical procedure. This all adds up to a remarkably low rate of complications compared to the literature; particularly when considering that 15 patients with giant adenomas were included (24,43,44,45).

Our results show that previous pituitary surgery elevates the risk of postoperative newly diagnosed pituitary insufficiency as all patients with new need for postoperative hormone substitution therapy had revision surgery for tumor regrowth or remnant. Interestingly those 5 patients (3.4%) had tumors of Hardy classification A or B only, which means that tumor size seems to be less of a risk factor for newly developing postoperative pituitary insufficiency. Out of 124 patients with first time pituitary surgery there was not a single case with postoperative newly developed pituitary insufficiency but 5 out of 24 patients with revision surgery showed newly developed pituitary insufficiency. Another factor explaining these results is that patients with Hardy classification D and E had a higher percentage of pituitary insufficiency already before surgery (72.2%) compared to Hardy classification A, B and C patients (24.4%).

Cavernous sinus infiltration of PAs seems to be a sign of greater tumor expansion but interestingly did not lead to higher rates of pituitary insufficiency, possibly since this does not mean more compression of healthy pituitary tissue in all cases. There were only 35.5% of patients with preoperative pituitary insufficiency showing cavernous sinus infiltration. In the complete study population there were 50 patients (33.8%) with cavernous sinus infiltration as well. Out of the 38 patients with postoperative persisting pituitary insufficiency there were 14 patients (36.8%) with cavernous sinus infiltration and out of the 24 patients with no further pituitary insufficiency there were 8 patients (33.3%) with cavernous sinus infiltration. These results suggest that cavernous sinus infiltration is not a risk factor for pituitary insufficiency.

There were some general limitations in this study that need to be thought of. iMRI was thought to be helpful in surgery and to improve outcome so that it seemed unethical to perform surgery without iMRI in part of the study population. Pure endoscopic treatment of pituitary adenomas was not performed during the time of this study so that there is no group of patients for comparison of the results within the same center. This is especially a drawback as comparison to previously published series is complicated as not only the surgical method but also pre- and postoperative study protocols differ widely.

Although the iMRI was useful and lead to improved remission rates and improved endocrinological- and neurological outcome there are some drawbacks in ultra-low field

iMRI to consider as well. Even if studies failed to show better results in surgical series using intraoperative high field MRI, image quality and resolution is - at least theoretically – better than in ultra-low field MRI (23,41). Costs for intraoperative imaging are still high due to installation, maintenance and time loss during surgery. Studies with larger patient numbers and cost/risk analysis should address the question whether better clinical and endocrinological outcome can compensate for these increasing costs.

7. Conclusions:

Data from this largest study to date analyzing general postoperative outcome and pituitary function in patients undergoing ultra-low-field iMRI-assisted microsurgical treatment of PAs show that the presented method is a safe and highly effective treatment option. The results are at least as good as those reported in previously published series – even in those with use of high-field iMRI or endoscopy. iMRI appeared to increase the rate of remission while keeping the complication rate low. Postoperative pituitary function was usually preserved and even improved in around 17% of the patients - possibly due to more exact and more extended iMRI-assisted tumor removal. This is not only a great achievement for each individual patient but also an important socioeconomic factor as hormone substitution therapy is expensive and health care systems worldwide face increasing budget deficits.

8. Table and figure legends

- Table 1: Study and patients characteristics
- Table 2: Pre-,intra- and postoperative imaging
- Table 3: Mean pre-/postoperative hormone levels
- Table 4: Characteristics of 62 patients with preoperative hypopituitarism: Type of deficiencies and replacement therapy before and after surgery
- Table 5: Endocrine outcome of patients grouped according to Hardy's classification

Illustrative case: Preoperative, intraoperative and postoperative imaging

- Figure A: Preoperative MRI, coronal view, contrast enhanced
- Figure B: Intraoperative MRI, coronal view, contrast enhanced, before skin incision
- Figure C: Intraoperative MRI, coronal view, contrast enhanced, during resection
- Figure D: Intraoperative MRI, coronal view, contrast enhanced, before closure
- Figure E: Postoperative MRI, coronal view, contrast enhanced

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Table 1: Study and patients characteristics

Number of patients	145
Number of operations	148
Sex (male/female)	82 / 63 (56.6% / 43.4%)
Mean age in years	55 \pm 15 (19-80)
Mean preoperative tumor size in mm ³	6797 (50-65,450)
Infiltration of cavernous sinus	51 (35.7%)
Patients with microadenoma	10 (6.9%)
Patients with macroadenoma	118 (82.5%)
Patients with giant adenoma	15 (10.5%)
Patients with previous surgery	24 (16.8%)
Patients with cranial nerve symptoms	89 (62.2%)
Patients with visual field deficits	79 (55.2%)
Patients with pan-/hypopituitarism	62 (41.9%)
Patients with preop. hormone substitution	29 (17.5%)

Table 2: Pre-,intra- and postoperative imaging

Preoperative tumor size in mm ³	6797 (50-65,450)
Infiltration of cavernous sinus	51 (35.7%)
Intraoperative imaging p.pt.	2.51 ± 0.99
Intraoperative additional tumor removal	56 (37.8%)
Mean follow up in month	32 (4-62)
Postoperative tumor remnant in mm ³	42 (28.4%)
Mean Size of tumor remnant in mm ³	1191 (4-15559)
Patients being in remission	101 (68.2%)

Table 3: Mean pre-/postoperative hormone levels

	preoperative	postoperative
Cortisol in nmol/l	393 (3-1640)	349 (9-808)
TSH in mU/l	1.73 (0.01-6.96)	1.72 (0.01-6.12)
fT4 in pmol/l	13.80 (5.60-20.30)	15.35 (4.00-25.40)
GH (NFPA pts only) in µg/l	0.59 (0.05-4.88)	1.21 (0.08-5.55)
IGF1 (NFPA pts only) in µg/l	102 (31-492)	101 (29-209)
Prolactin in µg/l	25.07 (0.50-109.50)	15.38 (0.50-227.00)
FSH (female pts only)	21.86 (0.10-92.00)	27.69 (1.20-95.90)
LH (female pts only)	9.29 (0.10-43.90)	12.78 (0.10-48.20)
Testosterone (male pts only) in nmol/l		